(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74414 A1

(51) International Patent Classification[7]: A61L 27/54, 29/16, 31/16, 27/34, 29/08, 31/10

(21) International Application Number: PCT/US01/40223

(22) International Filing Date: 2 March 2001 (02.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/540,242 31 March 2000 (31.03.2000) US
09/621,123 21 July 2000 (21.07.2000) US

(71) Applicant: ADVANCED CARDIOVASCULAR SYSTEMS, INC. [US/US]; 3200 Lakeside Drive, Santa Clara, CA 95054 (US).

(72) Inventors: BHAT, Vinayak, D.; 659 W. Homestead Road, Apt. #3, Sunnyvale, CA 94087 (US). HOSSAINY, Syed, F., A.; 34325 Tupelo Street, Fremont, CA 94555 (US). MIRZAEE, Daryush; 629 Ashbourne Drive, Sunnyvale, CA 94087 (US). MANDRUSOV, Evgenia; 3834 West Rincon Avenue, Campbell, CA 95008 (US). SANDERS-MILLARE, Deborra; 1430 Santa Inez Drive, San Jose, CA 95125 (US). GURUWAIYA, Judy, A.; 2074 Laddie Way, San Jose, CA 95121 (US).

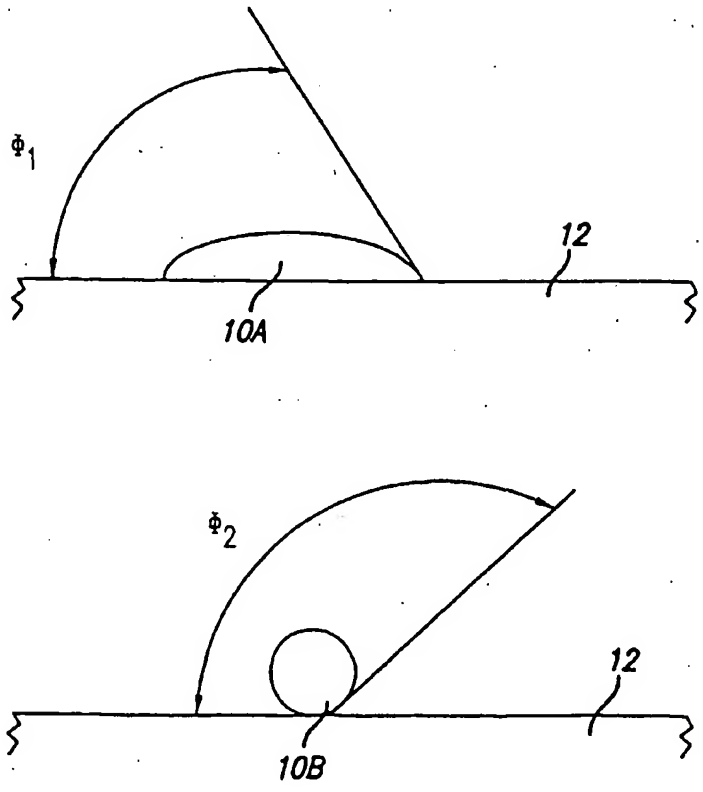
(74) Agents: KERRIGAN, Cameron et al.; Squire, Sanders & Dempsey L.L.P., 600 Hansen Way, Palo Alto, CA 94304-1043 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: A BIOCOMPATIBLE CARRIER CONTAINING ACTINOMYCIN D AND A METHOD OF FORMING THE SAME



(57) Abstract: A biocompatible carrier and a composition for forming the carrier are disclosed. The carrier is made from an ethylene vinyl alcohol copolymer which can serve as a reservoir, allowing for the local delivery and sustained release of actinomycin D. The carrier can be formed from the ethylene vinyl alcohol copolymer, a dimethylsulfoxide solvent, and actinomycin D. Alternatively, the carrier can be formed from an ethylene vinyl alcohol copolymer, a dimethylsulfoxide solvent, actinomycin D, and a wetting fluid. The carrier can serve as a coating for a prosthesis, for example a stent. The composition is applied to a surface of the prosthesis and essentially all of the dimethylsulfoxide solvent or dimethylsulfoxide solvent/wetting fluid is removed or allowed to evaporate to form the coating.

WO 01/74414 A1

A BIOCOMPATIBLE CARRIER CONTAINING ACTINOMYCIN D AND A METHOD OF FORMING THE SAME

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a biocompatible carrier containing an active ingredient for introducing the active ingredient to certain target cell population in a vascular region, such as smooth muscle cells, requiring modulation to ameliorate a diseased state, particularly for the treatment of stenosis or restenosis following a vascular trauma or disease. Moreover, the invention is directed to a composition, for coating an implantable device, containing actinomycin D, or analogs and derivatives thereof.

Description of the Background

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress the atherosclerotic plaque of the lesion against the inner wall of the artery to dilate the lumen. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results.

One proposed method for medicating stents disclosed seeding the stents with endothelial cells (Dichek, D.A. et al. Seeding of Intravascular Stents With Genetically Engineered Endothelial Cells; Circulation 1989; 80: 1347-1353). Briefly, endothelial cells were seeded onto stainless steel stents and grown until the stents were covered. The cells were therefore able to be delivered to the vascular wall where they provided therapeutic proteins. Another proposed method of providing a therapeutic substance to the vascular wall included use of a heparin-coated metallic stent, whereby a heparin coating was ionically or covalently bonded to the stent. Significant disadvantages associated with the aforementioned methods include significant loss of the therapeutic substance from the body of the stent during delivery and expansion of the stent, and an absolute lack of control of the release rate of the therapeutic substance from the stent.

Another proposed method involved the use of a polymeric carrier coated onto the surface of a stent, as disclosed in U.S. Patent No. 5,464,650 issued to Berg et al. Berg disclosed applying to a stent body a solution which included a specified solvent, a specified polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend. The solvent was allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer. Among the specified, suitable choices of polymers listed by Berg, empirical results were specifically provided for poly(caprolactone)

of administering the compositions, for inhibiting smooth muscle cell hyper-proliferation for the effective treatment of restenosis.

SUMMARY OF THE INVENTION

In accordance with one embodiment of the invention a coating for a prosthesis is provided. In one embodiment, the coating comprises an ethylene vinyl alcohol copolymer and actinomycin D or analogs or derivatives thereof. In another embodiment, the coating additionally comprises a therapeutic agent used in combination with actinomycin D or analogs or derivatives thereof. The prosthesis can be a balloon-expandable stent, a self-expandable stent or a graft.

In accordance with another embodiment, a method for forming a coating onto a surface of a prosthesis, e.g., a stent, is provided. In one embodiment, the method comprises applying to the surface of the prosthesis a composition which includes an ethylene vinyl alcohol copolymer and actinomycin D, or analogs or derivatives thereof. In another embodiment, the composition additionally includes a therapeutic agent used in combination with the actinomycin D.

The composition can include a fluid. In one embodiment the fluid is a dimethylsulfoxide solution. The ethylene vinyl alcohol copolymer can constitute from about 0.1% to about 35%, the dimethylsulfoxide solution can constitute from about 59.9% to about 99.8%, and the actinomycin D, alone or in combination with the therapeutic agent, can constitute from about 0.1% to about 40% by weight of the total weight of the composition.

In accordance with another embodiment, a fluid can include the dimethylsulfoxide solution and a wetting fluid. To enhance the wetting of the

elimination, for example, by heating the prosthesis at a predetermined temperature for a predetermined duration of time.

In accordance with another embodiment, a composition is provided for treating or inhibiting the narrowing of the blood vessel. The composition includes ethylene vinyl alcohol copolymer and actinomycin D, or analogs and derivatives thereof. The therapeutic composition is capable of being deposited in a selected region of the blood vessel to treat or inhibit the narrowing of the blood vessel.

In accordance with another embodiment, a therapeutic method is provided for inhibiting restenosis of a blood vessel by deposition into a designated region of the blood vessel an ethylene vinyl alcohol copolymer carrier impregnated with actinomycin D, or analogs and derivatives thereof.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1A illustrates a fluid on a solid substrate having a contact angle Φ_1;

Figure 1B illustrates a fluid on a solid substrate having a contact angle Φ_2;

Figure 2 graphically illustrates elution profiles for stents with a coating of ethylene vinyl alcohol copolymer impregnated with vinblastine made according to Example 4;

Figure 3 graphically illustrates in vitro experimental data, in accordance with Example 16, showing affects of actinomycin D, mitomycin, and docetaxel on smooth muscle cell proliferation;

27% to about 44%. Typically, 44 mole percent ethylene is suitable. As a general rule, an increase in the amount of the ethylene comonomer content decreases the rate that a therapeutic substance is released from the matrices of the copolymer. The release rate of a therapeutic substance decreases as the hydrophilicity of the polymer decreases. An increase in the amount of the ethylene comonomer content decreases the hydrophilic nature of vinyl alcohol comonomer. Ethylene vinyl alcohol copolymers are available commercially from companies such as Aldrich Chemical Company, Milwaukee, Wis., or EVAL Company of America, Lisle, IL, or can be prepared by conventional polymerization procedures that are well known to one of ordinary skill in the art. Typically, the ethylene vinyl alcohol copolymer can comprise from about 0.1% to about 35%, usefully from about 12% to about 20% by weight of the total weight of the composition. Typically, the DMSO solvent can comprise from about 65% to about 99.9%, usefully from about 80% to about 88% by weight of the total weight of the composition. A specific weight ratio is dependent on factors such as the material from which the prosthesis is made and the geometrical structure of the prosthesis.

In accordance with another embodiment, a fluid can be added to the composition which can enhance the wetting of the composition. To enhance the wetting of the composition, a suitable fluid typically has a high capillary permeation. Capillary permeation or wetting is the movement of a fluid on a solid substrate driven by interfacial energetics. Capillary permeation is quantitated by a contact angle, defined as an angle at the tangent of a droplet in a fluid phase that has taken an equilibrium shape on a solid surface. A low contact angle means a higher wetting liquid. A suitably high capillary permeation corresponds to a

weight of the total weight of the solution. Dimethylformamide used as the wetting fluid can comprise from about 1% to about 80%, usefully about 8% by weight of the total weight of the solution. 1-butanol used as the wetting fluid can comprise from about 1% to about 33%, usefully about 9% by weight of the total weight of the solution. N-butyl acetate used as the wetting fluid can comprise from about 1% to about 34%, usefully about 14% by weight of the total weight of the solution. Dimethyl acetamide used as the wetting fluid can comprise from about 1% to about 40%, usefully about 20% by weight of the total weight of the solution.

Active Ingredient

In accordance with another embodiment, sufficient amounts of an active ingredient are dispersed in the blended composition of the ethylene vinyl alcohol copolymer and the DMSO solvent, without the wetting fluid. In this embodiment, the ethylene vinyl alcohol copolymer can comprise from about 0.1% to about 35%, usefully from about 12% to about 20% by weight of the total weight of the composition, the DMSO solvent can comprise from about 59.9% to about 99.8%, usefully from about 79% to about 87% by weight of the total weight of the composition, and the active ingredient can comprise from about 0.1% to about 40%, usefully from about 1% to about 9% by weight of the total weight of the composition. More than 9% by weight of the active ingredient can adversely affect characteristics that are desirable in the polymeric coating, such as adhesion of the coating to the prosthesis. Selection of a specific weight ratio of the ethylene vinyl alcohol copolymer and the DMSO solvent is dependent on factors such as

amount of the active ingredient. The active ingredient should be in true solution or saturated in the blended composition. If the active ingredient is not completely soluble in the composition, operations including mixing, stirring, and/or agitation can be employed to effect homogeneity of the residues. The active ingredient can also be first added to the wetting fluid prior to admixing with the composition. The active ingredient may be added so that dispersion is in fine particles. The mixing of the active ingredient can be conducted in an anhydrous atmosphere, at ambient pressure, and at room temperature such that supersaturating the active ingredient is not desired.

The active ingredient should inhibit the activity of vascular smooth muscle cells. More specifically, the active ingredient is aimed at inhibiting abnormal or inappropriate migration and proliferation of smooth muscle cells.

"Smooth muscle cells" include those cells derived from the medial and adventitia layers of the vessel which proliferate in intimal hyperplastic vascular sites following vascular trauma or injury. Under light microscopic examination, characteristics of smooth muscle cells include a histological morphology of a spindle shape with an oblong nucleus located centrally in the cell with nucleoli present and myofibrils in the sarcoplasm. Under electron microscopic examination, smooth muscle cells have long slender mitochondria in the juxtanuclear sarcoplasm, a few tubular elements of granular endoplasmic reticulum, and numerous clusters of free ribosomes. A small Golgi complex may also be located near one pole of the nucleus.

"Migration" of smooth muscle cells means movement of these cells in vivo from the medial layers of a vessel into the intima, such as may also be studied in

fluoroscopy imaging, fiber optic visualization, or biopsy and histology. Biologically mediated vascular injury includes, but is not limited to injury caused by or attributed to autoimmune disorders, alloimmune related disorders, infectious disorders including endotoxins and herpes viruses such as cytomegalovirus, metabolic disorders such as atherosclerosis, and vascular injury resulting from hypothermia and irradiation. Mechanical mediated vascular injury includes, but is not limited to vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous transluminal coronary angioplasty, vascular surgery, stent placement, transplantation surgery, laser treatment, and other invasive procedures which disrupted the integrity of the vascular intima or endothelium. The active ingredient of the invention is not restricted in use for therapy following vascular injury or trauma; rather, the usefulness of the active ingredient will also be determined by the ingredient's ability to inhibit cellular activity of smooth muscle cells or inhibit the development of restenosis.

In one embodiment, the active ingredient is actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, WI 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. Actinomycin D is represented by the molecular formula $C_{62}H_{86}N_{12}O_{16}$, and is generally depicted by the following structure:

arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of suitable cytostatic or antiproliferative agents include angiopeptin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL (available from Squibb), CILAZAPRIL (available from Hoffman-LaRoche), or LISINOPRIL (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonist, LOVASTATIN (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available form Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone. Exposure of the ethylene vinyl alcohol/DMSO composition or ethylene vinyl alcohol/DMSO/wetting fluid composition to the therapeutic agent is not permitted to adversely alter the agent's composition or characteristic. Accordingly, the particular therapeutic agent is selected for mutual compatibility with the blended composition.

The dosage or concentration of the active ingredient required to produce a favorable therapeutic effect should be less than the level at which the active

20% nickel, 20% chromium, and 10% molybdenum. Prostheses made from bioabsorbable or biostable polymers could also be used with the blended composition. A polymeric prosthesis should be compatible with the composition. The ethylene vinyl alcohol copolymer, however, adheres very well to metallic materials, more specifically to stainless steel.

Methods For Coating the Prosthesis Using The Composition

To form a coating on a surface of the prosthesis, the surface of the prosthesis should be clean and free from contaminants that may be introduced during manufacturing. However, the surface of the prosthesis requires no particular surface treatment to retain the applied coating. The composition can be applied to both the inner and outer (the tissue contacting) surfaces of the prosthesis. Application of the composition can be by any conventional method, such as by spraying the composition onto the prosthesis or immersing the prosthesis in the composition. The addition of a wetting fluid leads to a consistent application of the composition which causes the coating to be uniformly deposited on the surface of the prosthesis.

After the composition is applied, the prosthesis can be heated by, for example, passing the prosthesis over a hot plate. The prosthesis should be exposed to the heat for a short duration of time, typically about 3 to 5 seconds. The temperature of the hot plate can be from about 55° C to about 65° C, typically about 60° C. Exposure of the prosthesis to the hot plate prevents the prosthesis from cooling at a rapid rate. Rapid cooling of the prosthesis may adversely affect properties that are generally desirable in a coating, such as elasticity. The polymer

during delivery and, if applicable, expansion of the prosthesis, but also controlled administration of the active ingredient following implantation. By way of example, and not limitation, the impregnated ethylene vinyl alcohol copolymer can have a thickness of about 0.5 microns to about 1.5 microns. The particular thickness of the copolymer is based on the type of procedure for which prosthesis is employed and the amount of the active ingredient that is desired to be delivered. The amount of the active ingredient to be included on the prosthesis can be further increased by applying a plurality of coating layers onto the prosthesis. The application of each layer should be performed subsequent to the evaporation of the DMSO solvent or DMSO/wetting fluid and the drying of the copolymer of the previous layer.

In one embodiment, a layer or a second coating formed from a polymeric material, free from the active ingredient or any therapeutic agents, is deposited on the active ingredient impregnated copolymer coating. Yet in another embodiment, a layer or a second coating formed from a polymeric material carrying at least one therapeutic agent, such as the aforementioned therapeutic agents, is deposited on the active ingredient impregnated copolymer coating. Suitable polymeric material can include, but are not limited to, polycaprolactone (PCL), poly-D,L-lactic acid (DL-PLA), poly-L-lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly (amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates,

content of the second coating decreases the rate that the active ingredient can permeate through the second coating. By way of example, and not limitation, the second coating can have a thickness of about 0.25 microns to about 1.5 microns. Typically, the second coating can have a thickness of about 1 micron. It is understood by one of ordinary skill in the art that the thickness of the layer is based on factors such as the type of procedure for which the prosthesis is employed and the rate of release that is desired.

Method of Use

In accordance with the above described method, the active ingredient can be applied to a prosthesis, e.g., a stent, retained on the stent during delivery and expansion of the stent, and released at a desired control rate and for a predetermined duration of time at the site of implantation. The release rate of the active ingredient can be controlled by modifying release parameters such as the amount of ethylene comonomer content of the copolymer and the initial active ingredient content in the copolymer. The rate of release can also be adjusted by the addition of second polymeric layer, with or without the active ingredient. A stent having the above described medicated coating is useful for a variety of medical procedures, including, by way of example, treatment of obstructions caused by tumors in bile ducts, esophagus, trachea/bronchi and other biological passageways. A stent having the above described medicated coating is particularly useful for treating occluded regions of blood vessels caused abnormal or inappropriate migration and proliferation of smooth muscle cells, thrombosis, and restenosis. Stents may be placed in a wide array of blood vessels, both arteries

stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. The mixture was placed in a warm water shaker bath at 60° C for 24 hours. The solution was cooled and vortexed. The cleaned Multi-Link™ stents were dipped in the EVOH solution and then passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were heated for 6 hours in an air box and then placed in an oven at 60° C, under vacuum condition, and for 24 hours. The coated stents were expanded on a 4.0 mm angioplasty balloon. The coatings remained intact on the stents. The coatings were transparent giving the Multi-Link™ stents a glossy-like shine.

Example 2

Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 4 grams of DMSO, making an EVOH: DMSO ratio of 1:4. Dexamethasone was added to the 1:4 EVOH: DMSO solution. Dexamethasone constituted 9% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box and then placed in a vacuum oven at 60° C for 24 hours. The above-recited step was repeated twice. The average weight of the coating was 0.0003 gram, having an estimated dexamethasone content of 75 ug per stent. The coated stents were expanded on a

Example 4

Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. Vinblastine was added to the 1:7 EVOH:DMSO solution. Vinblastine constituted 2.5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box then placed in a vacuum oven at 60° C for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00005 gram, with an estimated vinblastine concentration of 12 microgram per stent. Some of the stents were sterilized by electron beam radiation. The sterilized and unsterilized vinblastine coated stents were tested for a 24 hour elution period by placing one sterilized and one unsterilized stent in 5 ml of phosphated saline solution (pH 7.4) at room temperature with rotational motion. The amount of vinblastine eluted was evaluated by High Performance Liquid Chromatography (HPLC) analysis. The results of this test are given below and plotted in Figure 2. The data indicates that electron beam radiation procedure does not interfere in the release of vinblastine from EVOH.

Example 5

Multi-Link™ stents were cleaned by placement in an ultrasonic bath of isopropyl alcohol solution for 10 minutes. The stents were dried and plasma cleaned in a plasma chamber. An EVOH solution was made with 1 gram of EVOH and 7 grams of DMSO, making an EVOH: DMSO ratio of 1:7. Cephalotaxin was added to the 1:7 EVOH: DMSO solution. Cephalotaxin constituted 5% by weight of the total weight of the solution. The solution was vortexed and placed in a tube. The cleaned Multi-Link™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3-5 seconds, with a temperature setting of about 60° C. The coated stents were cured for 6 hours in an air box then placed in a vacuum oven at 60° C for 24 hours. The above process was repeated twice, having a total of three layers. The average weight of the coating was 0.00013 gram, with an estimated cephalotaxin concentration of 33 ug. The stents were sterilized by electron beam radiation. Cephalotaxin/EVOH coated stents and EVOH-coated control stents were implanted in the coronary arteries of 4 pigs, generally in accordance to the procedure set forth in "Restenosis After Balloon Angioplasty-A Practical Proliferative Model in Porcine Coronary Arteries" by Robert S. Schwartz, et al., Circulation 82(6):2190-2200, Dec. 1990, and "Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: Results in a Porcine Model" by Robert S. Schwartz et al, J Am Coll Cardiol; 19:267-74 Feb. 1992. Results of the porcine artery study indicated that there was no significant difference between the

mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. The dissolved EVOH: DMSO solution was mixed with 24.6 grams of THF and 19.56 grams of DMSO. The solution was mixed then placed in the reservoir of an air pressured atomizing sprayer. Multi-Link Duet™ stents were sprayed while the stents rotated between 30 to 120 rpm. The spray time was dependent upon the flow rate of the sprayer. A flow rate between 1 to 20 mg/second required a stent to be sprayed between 1 to 30 seconds. The polymer coated Multi-Link Duet™ stents were heated in a forced air convection oven for 12 hours. The coatings were transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 8

Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. Various co-solvents were examined to determine which co-solvent would promote a thicker coating. These co-solvents were THF, DMF, 1-butanol, and n-butyl acetate. The formulation for the co-solvents was as follows. Three grams of dissolved EVOH: DMSO solution was mixed with 0.9 gram of THF; three grams of dissolved EVOH: DMSO solution was mixed with 0.39 gram of DMF; three grams of dissolved EVOH: DMSO solution was mixed with 0.5 gram of 1-butanol; and three grams of dissolved EVOH: DMSO solution was mixed with 0.68 gram of n-butyl acetate. The cleaned Multi-Link Duet™ stents, attached

coatings will be transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 10

Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH: DMSO ratio of 1:4. The mixture is placed in a warm water shaker bath at 60° C for 12 hours. The solution is mixed, then cooled to room temperature. A 9% by weight Dexamethasone solution is formulated as follows: 2.96 grams of the EVOH: DMSO solution is mixed with 0.29 gram of Dexamethasone, then 0.9 gram of THF is added. The cleaned Multi-Link Duet™ stents are attached to mandrel wires and dipped into the solution. The coated stents are passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner. It is predicted that the coatings will be transparent, giving the Multi-Link Duet™ stents a glossy-like shine.

Example 11

Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 4.75% by weight actinomycin D solution was formulated as

alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 6.45% by weight actinomycin D solution was formulated as follows: 680 milligrams of the EVOH: DMSO solution was mixed with 80 milligrams of actinomycin D, then 480 milligrams of DMF was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven for 2 hours. A second layer of coating was applied and cured in the above manner.

Example 14

Multi-Link Duet™ stents are cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution is made having an EVOH: DMSO ratio of 1:40. The mixture is placed in a warm water shaker bath at 60° C for 12 hours. The solution is mixed, then cooled to room temperature. A 0.60% by weight actinomycin D solution can be formulated as follows: 4920 milligrams of the EVOH: DMSO solution is mixed with 40 milligrams of Actinomycin D, then 2000 milligrams of THF is added. The cleaned Multi-Link Duet™ stents can be sprayed upon by the above formulation. The coated stents are cured in a forced air convection oven for 2 hours. A second layer of coating is applied and cured in the above manner.

with sizes ranging from 0.2-0.8 micron).

The preclinical animal testing was performed in accordance with the NIH Guide for Care and Use of Laboratory Animals. Domestic swine were utilized to evaluate effect of the drug on the inhibition of the neointimal formation. Each testing procedure, excluding the angiographic analysis at the follow-up endpoints, was conducted using sterile techniques. During the study procedure, the activated clotting time (ACT) was monitored regularly to ensure appropriate anticoagulation. Base line blood samples were collected for each animal before initiation of the procedure. Quantitative coronary angiographic analysis (QCA) and intravascular ultrasound (IVUS) analysis was used for vessel size assessment.

The vessels at the sites of the delivery were denuded by inflation of the PTCA balloons to 1: 1 balloon to artery ratio and moving the balloons back and forth 5 times. The drug was delivered to the denuded sites at 3.5 atm (3.61 Kg/sq cm) for 2 minutes using the microporous balloon catheters before stent deployment. The average volume of delivery was about 3.3 +/- 1.2 ml. Following drug delivery, stents were deployed at the delivery site such that final stent to artery ratio was 1.1: 1.

QCA and IVUS analyses were used for stent deployment guidance. Pre-stenting IVUS measurements of the lumen size at the targeted vessel sites were performed for determination of the balloon (size) inflation pressure. Quantitative analysis of the stented coronary arteries to compare pre-stenting, post-stenting, follow-up minimal luminal diameters, stent recoil, and balloon/stent to artery ratio were performed. Following stent implantation and final angiogram, all devices

	CONTROL	DOSE 1	DOSE 2	t test (significant if p<0.05)	
	0M	1E-05M	1E-04M		
	(n=9)	(n=10)	(n=7)	p~	p*
ANGIOGRAPHIC DATA (QCA)					
Percent Diameter Stenosis	48.8 +/- 9.8	36.8 +/- 9.7	32.3 +/- 11.7	0.02	0.01
	CONTROL	DOSE 1	DOSE 2	t test (significant if p<0.05)	
	0M	1E-05M	1E-04M		
	(n=27)	(n=30)	(n=21)	p~	p*
HISTOMORPHOMETRIC DATA					
Percent Stenosis (IEL area-lumen area)/IEL area	63.4 +/- 12.7	51.8 +/- 13.8	54.1 +/- 11.7	0.002	0.01
Residual Lumen (Lumen area)/IEL area	0.36 +/- 0.16	0.49 +/- 0.14	0.46 +/- 0.08	0.002	0.01

~ comparison between control and Dose 1

• comparison between control and Dose 2

The results of the in vitro and in vivo standard test procedures demonstrate that actinomycin D is useful for the treatment of hyper-

Example 18

Multi-Link Duet™ stents (13 mm in length) were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 3.75% by weight actinomycin D solution was formulated as follows: 60 milligrams of actinomycin D was dissolved in 310 milligrams of DMF, then 1.22 grams of EVOH: DMSO solution was added. The cleaned Multi-Link Duet™ stents were attached to mandrel wires and dipped into the solution. The coated stents were passed over a hot plate, for about 3 to 5 seconds, with a temperature setting of about 60° C. The coated stents were cured in a forced air convection oven at 60° C for 1 hour. A second layer of coating was applied in the above manner and cured in a forced air convection oven at 60° C for 4 hours. An average coating weight of about 270 micrograms with an average actinomycin D content of about 51 micrograms was achieved.

Example 19

Multi-Link Duet™ stents were cleaned in an ultrasonic bath of isopropyl alcohol for 20 minutes, then air dried. An EVOH stock solution was made having an EVOH: DMSO ratio of 1:4. The mixture was placed in a warm water shaker bath at 60° C for 12 hours. The solution was mixed, then cooled to room temperature. A 6.1% by weight actinomycin D solution was formulated as follows: 100 milligrams of actinomycin D was dissolved in 310 milligrams of

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

(c) said actinomycin D, or analogs or derivatives thereof, constituting from about 0.1% to about 40% by weight of the total weight of the composition;

wherein after said composition is applied to a surface of said prosthesis, said dimethylsulfoxide solvent is essentially removed from said composition on said prosthesis to form said coating.

5. The coating of Claim 2, wherein said coating is made form a composition comprising:

(a) said ethylene vinyl alcohol copolymer constituting from about 0.1% to about 35% by weight of the total weight of said composition;

(b) a dimethylsulfoxide solvent constituting from about 19.8% to about 98.8% by weight of the total weight of said composition;

(c) a fluid constituting from about 1% to about 80% by weight of the total weight of said composition; and

(d) said actinomycin D, or analogs or derivatives thereof, constituting from about 0.1% to about 40% by weight of the total weight of the composition;

wherein after said composition is applied to a surface of said prosthesis, said dimethylsulfoxide solvent and said fluid are essentially removed from said composition on said prosthesis to form said coating.

(c) said actinomycin D, or analogs or derivatives thereof, in combination with said therapeutic substance, constituting from about 0.1% to about 40% by weight of the total weight of the composition;

wherein after said composition is applied to a surface of said prosthesis, said dimethylsulfoxide solvent is essentially removed from said composition on said prosthesis to form said coating.

11. The coating of Claim 8, wherein said coating is made form a composition comprising:

(a) said ethylene vinyl alcohol copolymer constituting from about 0.1% to about 35% by weight of the total weight of said composition;

(b) a dimethylsulfoxide solvent constituting from about 19.8% to about 98.8% by weight of the total weight of said composition;

(c) a fluid constituting from about 1% to about 80% by weight of the total weight of said composition; and

(d) said actinomycin D or analogs and derivatives thereof, in combination with said therapeutic substance, constituting from about 0.1% to about 40% by weight of the total weight of the composition;

wherein after said composition is applied to a surface of said prosthesis, said dimethylsulfoxide solvent and said fluid are essentially removed from said composition on said prosthesis to form said coating.

18. A coating for a prosthesis produced in accordance with the method of Claim 17.

19. The method of Claim 17, wherein said fluid comprises dimethylsulfoxide.

20. The method of Claim 19, wherein said ethylene vinyl alcohol copolymer constitutes from about 0.1% to about 35% by weight of the total weight of said composition, said dimethylsulfoxide constitutes from about 59.9% to about 99.8% by weight of the total weight of said composition, and said actinomycin D, or analogs and derivatives thereof, constitutes from about 0.1% to about 40% by weight of the total weight of said composition.

21. The method of Claim 17, wherein said fluid comprises dimethylsulfoxide and a wetting fluid, said wetting fluid selected from a group of tetrahydrofuran, dimethylformamide, 1-butanol, n-butyl acetate, dimethyl acetamide, and mixtures thereof.

22. The method of Claim 21, wherein said ethylene vinyl alcohol copolymer constitutes from about 0.1% to about 35% by weight of the total weight of said composition, said dimethylsulfoxide solution constitutes from about 19.8% to about 98.8% by weight of the total weight of said composition, said wetting fluid constitutes from about 1% to about 80% by weight of the total weight of said

27. A therapeutic method, comprising inhibiting restenosis of a blood vessel by depositing into a designated region of the blood vessel an ethylene vinyl alcohol copolymer carrier impregnated with actinomycin D, or analogs or derivatives thereof.

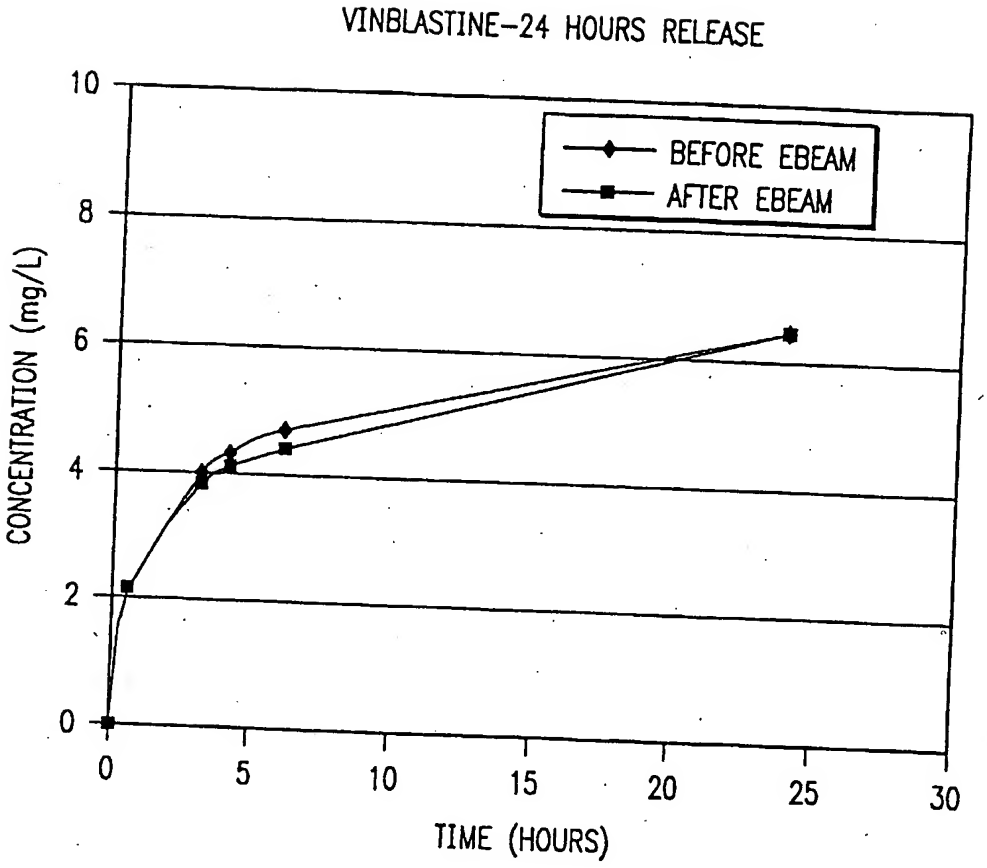

VINBLASTINE–24 HOURS RELEASE
BEFORE EBEAM
AFTER EBEAM
CONCENTRATION (mg/L)
0
2
4
6
8
10
0
5
10
15
20
25
30
TIME (HOURS)

FIG. 2

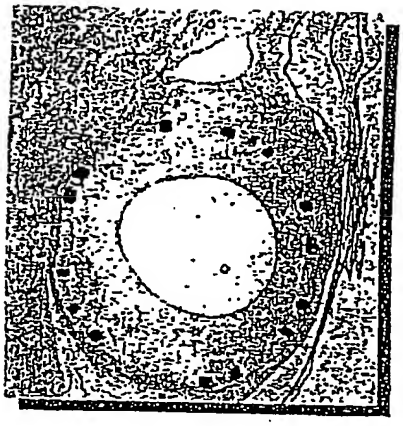


Figure 4A

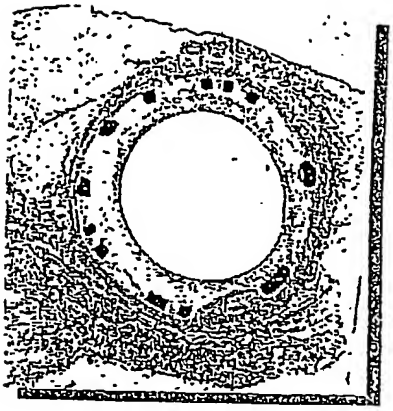


Figure 4B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/40223

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 45763 A (ADVANCED CARDIOVASCULAR SYSTEM) 28 June 2001 (2001-06-28) the whole document	1-27
A	US 4 977 901 A (OFSTEAD RONALD F) 18 December 1990 (1990-12-18) column 4, line 43 - line 44; claims	1-27
A	WO 99 63981 A (CERUS CORP) 16 December 1999 (1999-12-16) page 11, line 27; claims	1-27
A	US 5 800 392 A (RACCHINI JOEL R) 1 September 1998 (1998-09-01) column 11, line 33; claims	1-27
A	WO 97 45105 A (ANGIOTECH PHARM INC ;UNIV BRITISH COLUMBIA (CA); HUNTER WILLIAM L) 4 December 1997 (1997-12-04) page 5, line 27 - line 32 page 22, line 23	1-27